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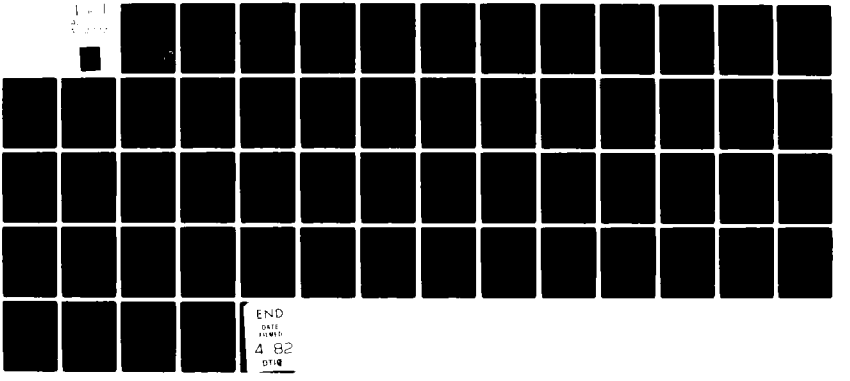

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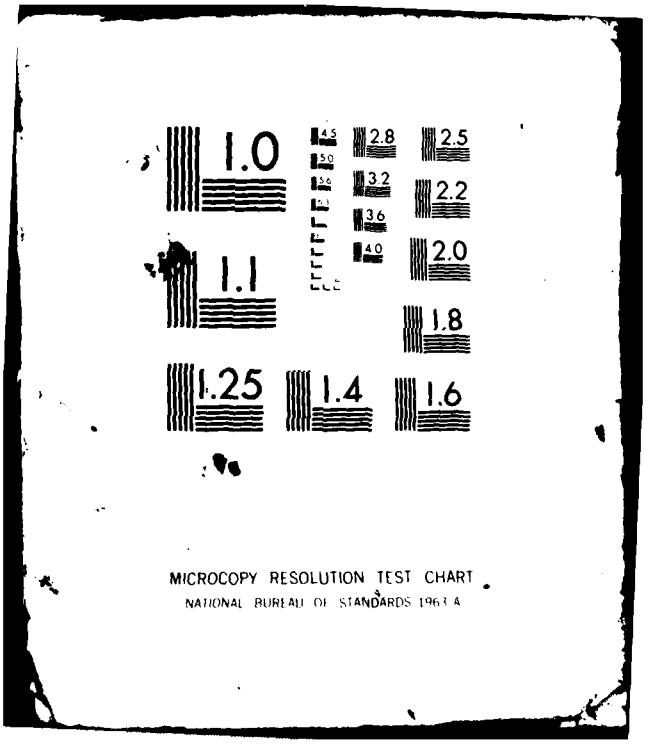
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MAMMALIAN TOXICOLOGY TESTING: PROBLEM DEFINITION STUDY

QUALITY ASSURANCE PLAN (U)

by
D. Y. Takade (Midwest Research Institute),
R. J. Davenport and R. H. Reuter

February, 1981

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract DAMD17-81-C-1013

Life Systems, Inc.
Cleveland, OH 44122

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Plans for the Quality Assurance requirements of an Applied Mammalian Toxicology Research/Testing Facility was prepared and summarized in this report. The plan included the Good Laboratory Practice regulations input. Permanent staffing recommendations are presented. The importance of Quality Assurance Standard Operating Procedures are noted.

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Report Subtitle	Life Systems, Inc. Report Number
Final Reports--	
Part 1. Comparative Analysis Report	LSI-TR-477-2
Part 2. Facility Installation Report	LSI-TR-477-3
Part 3. Impact of Future Changes Report	LSI-TR-477-4

FOREWORD

Reports for this Contract, DAMD17-81-C-1013, consist of three major final reports and twelve supporting documents. The Contract title, MAMMALIAN TOXICOLOGY TESTING: PROBLEM DEFINITION STUDY, is the main title for all the reports. Individual reports are subtitled and referenced with Life Systems, Inc. report numbers as detailed below. Please note that the Life Systems report numbers in test references are shortened. In the Defense Technical Information Center (DTIC) data base the reports are identified by the complete report numbers (i.e., LSI-TR-477-XXX) and complete numbers must be used for retrieval.

Report Subtitle	Life Systems, Inc. Report Number
Final Reports--	
Part 1. Comparative Analysis Report	LSI-TR-477-2
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Part 3. Impact of Future Changes Report	LSI-TR-477-4
Supporting Documents--	
Technology Changes Impact on Testing Requirements	LSI-TR-477-14
Quality Assurance Plan	LSI-TR-477-17A
Capability Modules	LSI-TR-477-19B
Technical Plan	LSI-TR-477-20A
Equipment Plan	LSI-TR-477-21A
Personnel Plan	LSI-TR-477-23A
Inhalation Chambers and Supporting Equipment Survey	LSI-TR-477-26A
Equipment List for Modules	LSI-TR-477-28B
AMTR Protocol/Pricing Report	LSI-TR-477-29A
Global Army Toxicology Requirements	LSI-TR-477-31A
Comparison Toxicology Test Costs	LSI-TR-477-36A
Annual Testing Capacity	LSI-TR-477-38A

SUMMARY

The Applied Mammalian Toxicology Research/Testing Facility will be a full-capability mammalian toxicology research and testing facility. As such, much of its key functions will come under the Good Laboratory Practice regulations. The purpose of these regulations is to assure that tests to prove the safety of medical or health-related materials are performed in accordance with acceptable procedures, and that the study data are of suitable quality and integrity.

The Good Laboratory Practice regulations require the creation of a Quality Assurance Unit and also specify the functions and procedures to be followed by the Quality Assurance Unit in assuring that the Facility's studies are in conformance with Good Laboratory Practice. For example, the Quality Assurance Unit must be independent of the line of management which is responsible for conducting the research and testing studies.

There are compelling management reasons why the Quality Assurance Unit should also be assigned responsibility for a Facility-wide Quality Assurance program aimed at assuring that the Facility's policies and procedures are being adhered to, as well as the Good Laboratory Practice regulations. Life Systems recommends, as do others,[a] that the Applied Mammalian Toxicology Research/Testing Facility's Quality Assurance Unit be given this broader role.

Permanent staffing for the Quality Assurance Unit is recommended to be on the lean side since some Quality Assurance functions will be performed by scientific staff of the Facility's Toxicology Research/Testing Directorate and Supporting Services. Analytical chemistry services needed in Quality Assurance can be obtained in-house or from external sources. Equipment maintenance and calibration can, in many cases, be provided by equipment manufacturers under service contracts.

One of the Quality Assurance Unit's most important functions will be to prepare the Facility's Quality Assurance standard operating procedures and participate in the preparation of the toxicology research/testing standard operating procedures. About 200 Quality Assurance standard operating procedures alone have been identified; all must be written and tested before the Facility can begin operations. Many hundreds of research/testing standard operating procedures will also be required. As a result of this large effort, Life Systems recommends that an important criterion in the selection of a Government Owned Contractor Operated contractor for the Facility be that it already have access to standard operating procedures which could be easily adapted to the Facility's needs.

Although not required by the Good Laboratory Practice regulations, Life Systems recommends that the Quality Assurance Unit should also have a review/edit/approval role in the preparation of research/testing protocols. Such a procedure has been shown to be useful and valuable in similar facilities. This report contains guidelines for the Quality Assurance Unit's other functions

(a) Fischbeck RD. 1980. Good laboratory practice regulations and their impact on laboratory organization and operation. Am. Lab. Sep.

such as handling and storage of test and control articles, Facility inspections regarding proper animal care, storage of data and specimens, report and master schedule files, the Quality Assurance Manual, performance evaluations of analytical chemists, generation of mangement reports, etc.

Writing Quality Assurance Standard Operating Procedures will require an estimated 14 months. If the selected contractor has Quality Assurance Standard Operating Procedures which only need be modified to fit the Facility's needs, then only about eight months will be required. Verification and implementation of the Quality Assurance Standard Operating Procedures will require an additional 26 months. Thus it can be seen that the earliest operational date for the Facility will be 34 months after contract award.

Preoperational Quality Assurance costs are estimated at $307,600. Continuing Quality Assurance costs in the operational phase are estimated to be 5-6% of the Applied Mammalian Toxicology Research/Testing Facility's annual budget per year.

Because operations cannot begin until a satisfactory Quality Assurance program is in place and approved by the Food and Drug Administration and Environmental Protection Agency, it will be important that the Quality Assurance startup and implementation activities remain on schedule.

FOREWORD

The Quality Assurance Plan described herein was developed by Life Systems, Inc. under U.S. Army Contract DAMD17-81-C-1013 during the period January 6, 1981 to March 20, 1981. The program was directed by Dr. R. A. Wynveen. The technical and administrative efforts were completed by Mr. D. Culver, Dr. R. J. Davenport, Mrs. D. Jones, Dr. D. Takade, Ms. P. Marcinko, Ms. C. D. Patrick, Ms. D. A. Ruschak and Dr. R. Wynveen.

Col. Allen was the Contracting Officer's Technical Representative for the Letterman Army Institute of Research, San Francisco, CA 94129.

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LIST OF ACRONYMS AND ABBREVIATIONS

ADPE	Automatic Data Processing Equipment
CV	Curriculum Vitae
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GOCO	Government Owned Contractor Operated
GLP	Good Laboratory Practice
MIS	Management Information System
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedure

INTRODUCTION

The Good Laboratory Practice (GLP) regulations of the Food and Drug Adminintration (FDA) and Environmental Protection Agency (EPA) require the creation of a Quality Assurance Unit (QAU) within facilities performing nonclinical toxicology research and testing. The purpose of the GLP's and QAU is to assure that studies to prove the safety of medical or health-related materials are conducted in accordance with acceptable practice, and that data from such studies are of suitable quality and integrity. However, the GLP's also form the basis of effective Quality Assurance (QA) programs for use in other research, as well.

The regulations are far-reaching in that they cover every operational aspect that impinges on the results of toxicological research and testing:

- Organization and personnel
- Facilities
- Equipment
- Procedures and protocols
- Testing operations
- Reports and records

Although the GLP regulations contain measures for enforcing adherence (including disqualification of testing facilities), their major impact has been to improve, strengthen, and standardize the quality of research data. And, while they have added significantly to the cost of toxicological research and testing, they also produce improved efficiency and management practices which offset at least a portion of the added costs. Costs incurred because of the need to reproduce flawed studies are also eliminated through the use of GLP.

There is no question that the Applied Mammalian Toxicology Research/Testing (AMTR) Facility will observe the GLP -- it is mandatory for at least part of the testing that can be anticipated for the Facility. For this testing, it is also mandatory that the Facility create a QAU, some of whose responsibilities are also mandated by the GLP. Accordingly, Task 6 of this Program was performed in order to prepare a QA Plan that will assure that planning for the Facility's operations will include considerations of GLP after the Facility is operational. The QA Plan will also ensure that the Facility's policies and procedures are adhered to during the conduct of toxicology research and testing.

Objectives

The objectives of the QA Plan are:

1. To provide a plan for organizing and implementing a QA Department for the AMTR Facility. The primary function of the QA Department will be to ensure that all toxicology research and testing complies with the Facility's QA requirements and GLP regulations.

2. To facilitate preparation of the necessary QA Manuals (i.e., separate QA Manuals may be required for different technical areas):

    a. To provide a systematic plan for their preparation
    b. To provide needed quidelines
    c. To minimize the time, effort, and cost for their preparation (e.g., avoiding the "reinventing the wheel" syndrome).

3. To budget resources required for QA activities, including GLP compliance:

    a. Personnel requirements
    b. Facilities, equipment and consumables

4. To project a schedule for implementing the QA function.

5. To estimate the costs of satisfying the QA requirements and GLP compliance.

Assumptions for the Quality Assurance Plan

The assumptions for the QA Plan are:

1. The Facility is to be a full capability mammalian toxicology research/testing facility.

2. The QA Manager will be on board at start up.

3. The Facility will conform to the FDA's GLP regulations and the EPA's proposed GLP regulations. It will undergo and pass FDA GLP inspections.

4. The Facility will be divided into the following six business functions (Figure 1):

    a. Administration
    b. Financial
    c. Legal/Contract Administration
    d. Product/Quality Assurance
    e. Toxicology Research/Testing Directorate
    f. Support Services Directorate

5. The Toxicology Research/Testing Directorate will include the following divisions/department/sections undertaking the related studies (including oral, inhalation, dermal and ocular exposures):

    a. General toxicology studies
    b. Behavioral toxicology studies
    c. Metabolism/pharmacokinetic studies
    d. Pharmacodynamics studies
    e. Oncogenic studies
    f. Respiratory physiology studies
    g. Reproduction studies

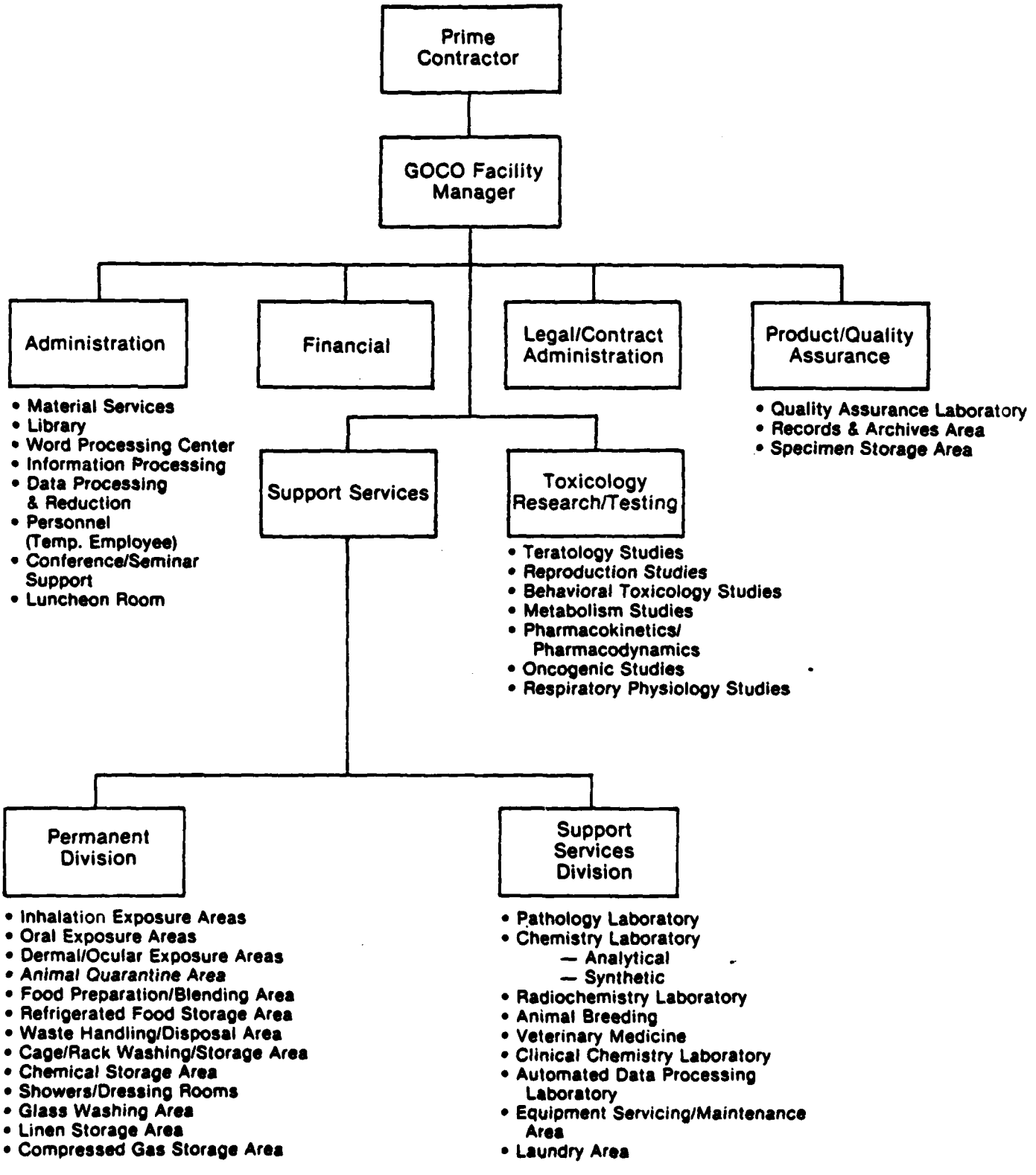


FIGURE 1 ORGANIZATIONAL LOCATION OF FACILITY LABS AND AREAS

h. Teratology studies
i. Neurotoxicology studies
j. Genetic toxicology studies

Interrelationships with Other Tasks

Task 6 of this Program interfaces with three other tasks in the Program:

1. Equipment - QA is responsible for establishing procedures for maintenance, calibration and inspection of all equipment used in the generation of toxicology research/testing information.

2. Facilities - QA is responsible for setting forth specifications so the Facility conforms with Government regulations concerning animal care, radiation safety and personnel occupational health.

3. Personnel - QA is responsible for assuring management that personnel qualifications, training and experience are documented and compatible with their job function.

Definitions

The following are established definitions related to QA (USEPA 1980, USEPA 1979, USEPA 1978, USFDA 1978):

1. Archives - The area used to store all raw data, notes, specimens, slides and other information generated as the result of a toxicology study.

2. Control Article - Any chemical, substance or mixture of materials that is administered to the test system in the course of a study for the purpose of establishing a basis for comparison (often used synonymously with Reference Standard).

3. Protocol - A detailed description of the design and technical conduct of a study.

4. Quality Assurance - A comprehensive system of plans, specifications and policies such as audits and inspections that are designed to ensure the collection, processing and reporting of data.

5. Quality Control - The system of activities designed to achieve and maintain a previously specified level of performance in data collection, processing and reporting.

6. Raw Data - Any laboratory worksheets, records, memoranda, notes, chromatograms or exact copies thereof, that are the result of original observations of a study.

7. Specimen - Any material derived from a test system for examination or analysis.

8. Test Article - A specific form of a chemical substance or mixture used to develop data (often used synonumously with Sample).

9. Test Mixture - A combination which results from mixing a test substance with another substance or substances (e.g., water, feed) for the purpose of exposing the test system.

10. Test System - The animal, microorganism or subpart thereof to which the test or control article is administered.

11. Test Facility - The establishment or organization person who actually conducts a nonclinical or toxicology study.

AMTR FACILITY AND ORGANIZATION

By its very nature, the QA function in a laboratory such as the AMTR Facility permeates the entire operation. The Facility's management should view this as an advantage, and capitalize on it by encouraging QAU participation in protocol development, research problem solving, interdepartmental liaison, overall QC, and even sponsor contact. In essence, the QAU will be management's and the sponsor's assurance that GLP's are being met. The QAU will scrutinize laboratory procedures from a management as well as from a scientific perspective.

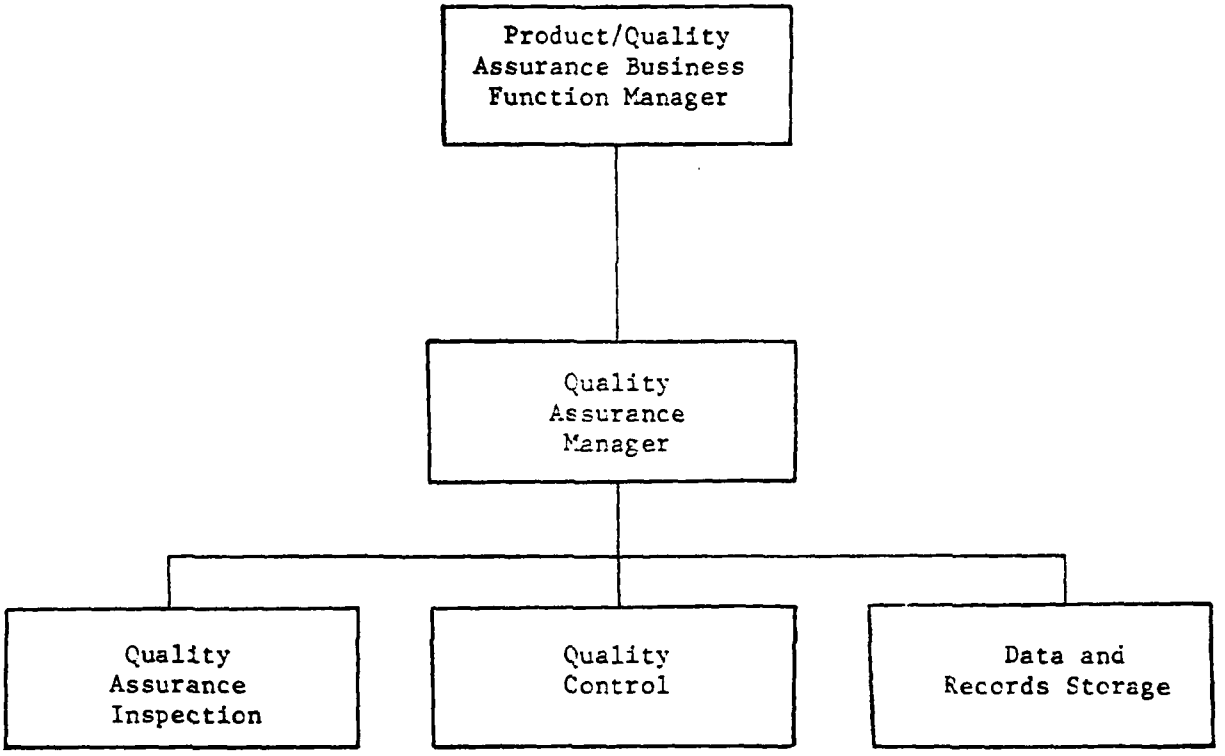
The QAU will help the laboratory in such areas as staff training, research and testing efficiency, and sponsor relations. Standardization, systematization, and documentation will produce a method -- independent of financial and scientific management -- of managing projects and data. Standardization and documentation will be, in fact, the major manifestations of GLP influence on the AMTR Facility's operations. They also will force management to review procedures, such as the use of computers for direct access to test animal weights, observations, and pathology data. This not only will reduce recording time and errors but will also make final report preparation more efficient.

Other efficiencies will arise out of data handling, storage, and retrieval. The sheer bulk of required data retention has created renewed interest in, and studies of, microfilming as a method of reducing storage costs. New developments in this area will be adopted by the AMTR Facility as they become available, after the appropriate cost/benefit evaluations.

In light of the foregoing, the AMTR Facility will develop an entire QA Program that includes GLP compliance as one of its basic parts. Thus, the desired result of the overall program will be determined and clearly defined before any SOP's are prepared. The overall plan will take into account the interactions between components of the AMTR Facility. It will also reflect the fact that FDA inspectors and study sponsors will be concerned with more than one of the Facility's components, and because of this, the QA systems must be standardized and uniform throughout the Facility.

QUALITY ASSURANCE DEPARTMENT DESCRIPTION

The organization of the functions with the QA Department (which serves the functions of the QAU mandated by GLP regulations) is illustrated in Figure 2. The QA business function is organized around the GLP regulations and guidelines,



- Facilities Inspection
- Equipment Inspection
- Audit Inspection

FIGURE 2 QUALITY ASSURANCE DEPARTMENT ORGANIZATION CHART

but also covers the internal QA requirements of the AMTR Facility. The QA Manager is directly responsible to the Product/Quality Assurance Business Function Manager of the Prime Contractor. The QA Manager is only indirectly responsible to the Facility Manager. This preserves the requirement of QA not report to personnel associated with or involved in a nonclinical or hazard evalutation study. There are three functions reporting to the QA Manager to ensure unbiased and independent judgments concerning the conduct and evaluation of these studies: (1) QA Inspections, (2) Quality Control (QC) and (3) Data and Records Storage.

Scope of Operation

The scope of operation of the QA Department is as follows:

1. Define, identify, prepare and implement procedures.
2. Assure GLP compliance and compliance with all other QA requirements by monitoring, inspecting and auditing all study phases.
3. Assure inspection, calibration and maintenance of all instruments and scientific equipment.
4. Establish and maintain a quality control and proficiency testing program in all areas utilizing quantitative analytical instrumentation.
5. Maintain the Record Archives Area in which all data generated as a result of a study will be stored.
6. Maintain a storage area for all test and control articles.
7. Receive, log and control all test and control articles.
8. Maintain primary certified weights and measures and ensure an ongoing certification program.
9. Maintain a QC Acceptance Program for all incoming consumables.
10. Maintain a complete file of all original SOP's and revisions as a historical file.
11. Establish and implement standard operating procedures (SOP's) for the conduct of QA internal inspections and inspections by the FDA, EPA and/or individual study sponsors.

Responsibilities

The QA Department is responsible for ensuring the facilities, equipment, personnel, methods, practices, records and all other pertinent elements of a study are in conformance with the QA requirements, GLP regulations and guidelines including:

1. Maintaining a copy of the master schedule sheet of all studies, including descriptive titles, nature of the study, start and projected completion dates, client status, study director's name and final report status.

2. Maintaining copies of all study protocols, including changes.

3. Periodically inspecting each phase of a study.

4. Maintaining written and signed records of each inspection, giving inspection date, study identity, phase, name of inspector, findings and problems, and any other recommendations or actions and reinspection dates.

5. Periodically submitting written status reports to management and the Study Director of each study inspection, noting any problems and recommended actions.

6. Determining if deviations from protocols or SOP's were made, and ensure that proper authorization and documentation exists.

7. Reviewing the final report to ensure the report accurately documents the efforts performed, the SOP's used and the raw data.

8. Preparing and signing the statement to be included with the final report which specifies inspection dates and dates of reports to management.

9. Ensure that any required corrective actions are taken in a timely manner.

Organizational Interrelationships

Because its responsibilities cut across much of the Facility's operations, the QA Department will, of necessity, be required to work closely with most other elements of the Facility. This will be particularly true with both branches of the Support Services Directorate because of the QA Department's responsibility to assure that the Facility conforms with GLP (and other regulations and guidelines) concerning animal care, occupational health, and radiation safety. These responsibilities will also require the QA Department to work closely with Purchasing, Central Utilities, and equipment specifiers and procurers.

The QA Department will interrelate with Personnel as a result of its role in assessing personnel performance as well as its responsibilities in health and safety matters.

QUALITY ASSURANCE DEPARTMENT PERSONNEL

Duties and Responsibilities

The following descriptions of the titles, duties and responsibilities and background are given for personnel who will be required to function in the QA Department.

Quality Assurance Manager

The QA Manager is responsible for direction, coordination and execution of the QA Scope of Operation (see above); defines QA/GLP requirements; ensures all aspects of GLP regulations and guidelines are met; assigns QA specific tasks to be conducted; prepares detailed implementation plans for QA activities; sets guidelines for technical training and documentation; identifies, defines and prepares specific QA SOP's and acts as focal point for coordination and distribution.

The QA Manager should possess a degree (B.S. plus ten years of experience, or M.S. plus seven years of experience) in a QA or Product Assurance related technical discipline, must be knowledgeable in FDA and EPA regulations concerning GLP, must possess a good working knowledge of toxicology and chemistry, and have two to four years prior QA/GLP experience.

Quality Assurance Inspector

The QA Inspector is responsible for carrying out the plans and programs initiated by the QA Manager with regard to facilities, equipment and audit inspection for QA/GOP compliance. The QA Inspector coordinates and supervises the activities of the QA Facilities Inspector, QA Equipment Inspector and QA Audit Inspector. The QA Inspector should possess a technical degree (B.S. plus seven years experience or M.S. plus five years experience) and prior experience in QA/GLP inspections, audits and SOP preparation and coordination.

The functions reporting to the QA Inspector are defined in greater detail below.

Facilities Inspector. The function of QA Facilities Inspection is responsible for determining and assuring that facilities associated with inhalation exposure, oral exposure, dermal/ocular exposure, animal quarantine, food preparation/blending and waste handling/disposal in all laboratory areas conform to Federal regulations (GSA 1981, GSA 1980, GSA 1979). The Facilities Inspection function secondarily serves other areas such as equipment, records, reports and studies. A Facilities Inspector should have previous experience and background in toxicology facility upkeep, inspections and animal welfare regulations. A B.S. degree in a technical discipline plus two to four years experience is required.

Quality Assurance Equipment Inspector. The primary duty of the QA Equipment Inspection function is to assure the proper inspection, maintenance, calibration of all technical equipment used in the conduct of a toxicology study. Secondarily, an Equipment Inspector may carry out the functions of inspecting facilities, records, reports and studies. An Equipment Inspector must be knowledgeable in the use and of maintenance analytical chemistry equipment and the use of toxicology support equipment. A B.S. degree in chemistry or related discipline plus two to four years experience is required.

Quality Assurance Audit Inspector. The primary duty of the QA Audit Inspection function is to validate toxicology studies by data trail audit to include corrective action and traceability of instruments, control articles, test articles and test systems. Secondarily, an Audit Inspector may act as an

inspector of facilities and equipment. An Audit Inspector should have a background in life sciences with some background in GLP inspection. A B.S. degree plus two to four years experience with emphasis in toxicology is desirable.

Quality Control Chemist

The QC Chemist is responsible for administering the chemistry proficiency testing program in the facility; maintaining the control article repository; preparing and assigning control article blind samples; receiving and reviewing the analytical data (this includes notebook information, chromatograms and other raw data) and determining if they are within performance specifications. The QC chemist maintains control charts and informs management of problem areas, and conducts a testing program to determine the acceptability of consumables.

The QC Chemist must possess a B.S. degree in chemistry plus five years experience, specifically QC chemistry, or an M.S. degree in chemistry with three years experience. The QC Chemist must be experienced and proficient in the analysis of organic and inorganic chemicals using a variety of analytical instruments and techniques.

Data and Records Storage Supervisor

The Data and Records Storage function is responsible for organizing and maintaining the data storage repository in a systematic fashion. This function checks out and maintains records of laboratory books, including their return; files, distributes and assists in updating SOP's. An Archives Supervisor should be very familiar with organizing and cataloging data and storage facilities. Knowledge of computer systems, as well as the handling and distributing potentially hazardous substances, is of great value.

Operational Requirements

It may be necessary to staff all the foregoing positions with full-time, permanent personnel. For example, data audits may utilize the statistical staff with the Research/Testing Directorate, rather than a full-time statistician with the QA Department. Similarily, it may be more economical to subcontract outside vendors to perform some of the costly and less frequently performed chemical analyses. Other analyses can be done by the staff in the Research/Testing Directorate who routinely perform these analyses.

The function of the QA Department, in such cases where the technical staff of the Research/Testing Directorate performs a QA function, will be to identify blind samples for analysis and to ensure that the analyses are done according to SOP's. The benefit of this approach is that it obviates the need to duplicate services, purchase additional equipment, and hire more personnel.

Similarly, inspections and audits can be performed by scientists in the Research/Testing Directorate so long as such individuals and supporting staff are not assigned to inspect or audit their own studies.

PROTOCOLS AND PROCEDURES

The GLP regulations require that each study have an approved written protocol that clearly indicates the objectives of the study and all the procedures planned for conducting it. There are 16 specific protocol requirements contained in the regulations. Regulations also require that SOP's be written which detail all operations employed by the facility in conducting studies.

The combined impact of protocol and procedural documentation can be enormous. Thousands of pages will be involved. Multiplying that number by the many copies needed to provide the documentation to all who require it can result in hundreds of thousands of pages. It is clearly imperative, therefore, that an effective system be developed which will constrain and control the entire procedure so that it does not become a burden.

Protocol Development

Three factors are important (in addition responding to the 16 specific protocol requirements) in developing study protocols:

- Protocol format
- Procedure reference
- Protocol approval

Protocol Format

A standardized format for study protocols will be developed. Its purpose will be to force protocol writers to place certain technical details into predetermined sections of the protocol. These sections will always be maintained in the same order relative to each other.

With this concept, users can find any specific bit of information in a lengthy protocol within seconds.

Procedure Reference

The protocol procedure will also require that specific SOP's be listed in the text of the protocol by their identification number. Thus, these identification numbers will uniquely and specifically identify the exact technical activities which are to be used in the study. This is a "shorthand" way of specifying a technique without having to write lengthy technical procedures into each study protocol.

Protocol Approval

Although only the study sponsor and the Study Director are required to approve new or amended protocols, Life Systems recommends that approval by the QA Department and at least one member of management also be required. This will help ensure that each key member of the Facility's management team will be aware of the requirements to be placed on the Facility and its personnel before any study starts.

SOP Development

Several types of SOP's will be required to describe the functions of the AMTR Facility, such as policy, administrative, technical operations, equipment operation and analytical methods. Written standard will be established for each of these types, and when each should be utlized. In effect, this will provide written procedures on how to prepare procedures for each of the facility's discrete operations. An example of such a procedure is shown in Appendix 1. Appendix 2 is a sample format for the preparation and content of SOP's.

The advantage of preparing procedures for writing is apparent when one considers that there will be hundreds of procedures required for the AMTR Facility. The result would be chaotic if each had a style and format different from every other.

The SOP system will not only satisfy the requirements of GLP regulations but also will be a valuable management tool. SOP's will minimize training efforts for new employees and will greatly reduce errors and misunderstandings concerning the proper procedural conduct of studies.

Once procedures covering preparation of SOP's are written and approved, the authorship of individual SOP's will be the responsibility of suitably qualified personnel who are designated to write them. All SOP's will be reviewed and edited by the QA Department which will also maintain the master file or manual of the SOP's protocols and amendments.

Appendix 3 contains a listing of titles of QA SOP's that will be required by the AMTR Facility. The following brief discussions summarize the salient points of each of the categories of SOP's contained in Appendix 3.

Facilities SOP's

These cover the specification, inspection, and sanitation of facilities used in toxicology testing. The SOP's must deal with lighting, ventilation, room dimensions, drainage, power and backup power as well as conforming to regulations related to animal health, radioactive materials, and employee health (GSA 1981, GSA 1980, GSA 1979). Special Army requirements include SOP's for testing smokes, obscurants, and other Army-unique chemicals, as well as unique test characteristics such as short-duration and high-concentration exposures.

Equipment SOP's

These are concerned with inspection, maintenance, and calibration of all equipment. The SOP's must address forms, charts and schedules required by manufacturers' or others' specifications.

Consumable SOP's

These involve screening all incoming chemicals, reagents, animal feed, etc., including vertification of manufacturers' specifications. These SOP's should include assay method, specifications, random sampling procedure, and reports of findings.

Automatic Data Processing Equipment (ADPE) SOP's

These address error prevention and detection. Error prevention embraces staff training, instrument and ADPE maintenance, diagnostic programs, check point programs, and test verification programs. Error detection includes program override, entry of check or dummy digits for comparison, and error message notification program.

ADPE may also be used to operate an automated inhalation chamber system which will require SOP's for chamber concentration and monitoring, and data recording.

Records SOP's

This covers storage and retrieval of raw data, specimens and computer tapes and discs, and addresses receipt, identification, completeness, indexing, archive security and access, and information, retrieval and checkout. Requirements for records have been published (USEPA 1980, USEPA 1979, USFDA 1978).

Traceability SOP's

These include instruments (identified by a unique inventory number), control articles (allowing for comparison to a known reference material such as a National Bureau of Standards (NBS) standard), test articles (establishing point of origin and comparison to its reference control article), animal test system (establishing origin, health, quarantine, receipt and final test disposition), and data (an audit trail allowing for the complete reconstruction of a study).

Test and Control Article SOP's

These involve handling, mixing and storage of test and control articles.

Performance Audit SOP's

These involve testing analysts' abilities by means of blind standard materials. They apply to clinical and analytical chemistry and other areas using equipment which yield quantative information. An example is provided in Appendix 4.

Corrective Action SOP's

This covers the flow of QA information, including provisions for corrective action when data quality falls below a protocol limit or when significant problems are encountered during a study.

Study Planning and Conduct SOP's

These include data recording, protocol preparation, protocol changes, and pre-study personnel changes.

Personnel SOP's

Documentation of training, sanitation and health precautions, protective clothing and devices, etc.

Animal care SOP's must conform to regulations (GSA 1979).

Other Documents Requiring Preparation

In addition to protocols and SOP's, other documents which need to be prepared for the AMTR Facility include position descriptions for personnel in Product/ Quality Assurance, the Support Services Directorate, and the Toxicology Research/ Testing Directorate. Such descriptions will be prepared by Personnel.

A position description will contain information on the following topics:

1. Preparation date
2. Position title
3. Department
4. Individual's supervisor
5. Personnel reporting to the individual
6. Duties and responsibilities
7. Position requirements:

    a. Education
    b. Experience
    c. Certification

Curriculum Vitae (CV) must be prepared for the personnel. All CV's should include additional and/or on-the-job training acquired by staff members. Particularly important is verification of training in performance of specific SOP's, health and safety requirements, etc. A format for the preparation of a CV is shown in Table 1.

Quality Assurance Manual

The QA Manual is the document that contains the QA SOP's and personnel documents described above. Appendix 5 is a typical Table of Contents for a Master QA Manual, which will contain all SOP's and personnel documents. The Master QA Manual will be used primarily only within the QA Department. Other departments within the AMTR Facility will be provided smaller QA Manuals that provide the information they need to perform their functions, but not other procedures and personnel documents they will not use. This approach is expected to minimize confusion, reduce the time required by Manual-users to find the information they need, and optimize their attitudes toward the QA function and Department.

FACILITIES

The facilities for the QA Department consist of the Quality Assurance Laboratory (given designation of Module No. 23 in the planned AMTR Facility) and the Record Archives Area (Module No. 40). Dimensions, planned arrangement of the major pieces of equipment, significant construction details and cost information are shown these modules in Figures 3 and 4, respectively.

Quality Assurance Laboratory

The QA Laboratory contains the analytical instrumentations for frequently performed analyses, a separate room for analytical balances and an office.

TABLE 1 CURRICULUM VITAE FORMAT

Name

Position Title

Education (may be more than 1)
- Degree
- Year
- Major/Minor
- University or College

Special Seminars, Workshops, Training (may be more than 1)
- Program
- Date
- Sponsoring Organization
- Certificate/Award

Professional Certifications, Licensure, Registration (may be more than 1)
- Title
- Year
- Board
- Registration/License Number
- State

Professional Affiliations (may be more than 1)

Honors and Awards (may be more than 1)
- Titles
- Source
- Location
- Year

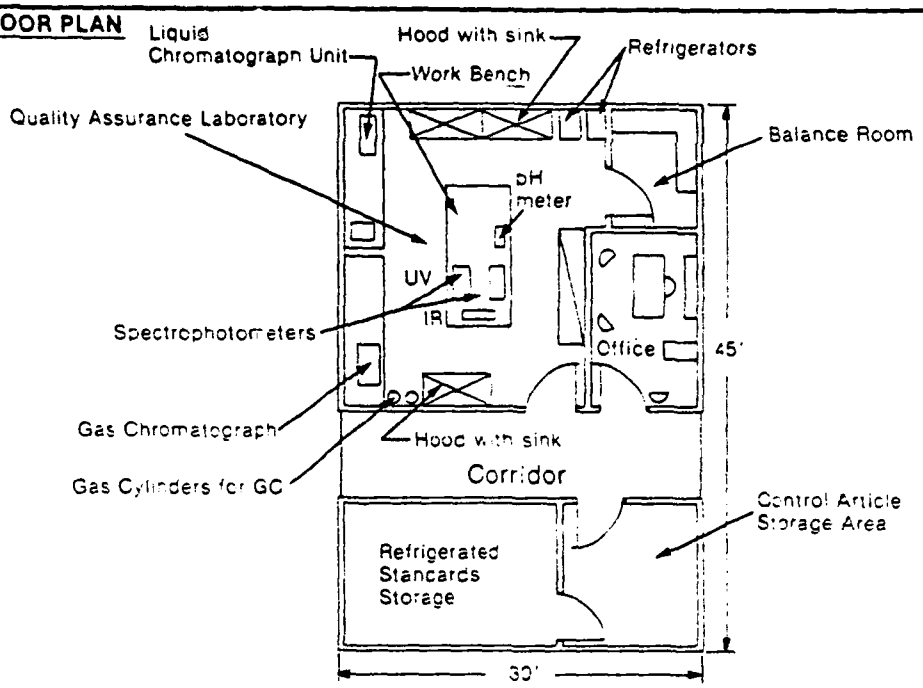
Professional Experience (specific answers required; list all positions held from most recent)
- Position Title:
- Company:
- Location:
- Date (mo/yr to mo/yr):
- Duties and Responsibilities:
- Special Skills:

Publications

MAMMALIAN TOXICOLOGY FACILITY MODULE DESCRIPTION

Life Systems

FLOOR PLAN



SCALE: 1" = 15'

CONSTRUCTION INFORMATION

Dimensions: 30 x 45 Ft.
Area: 1,350 Sq. Ft.
Ceiling Height ☐ 8' ☒ 9' ☐ 13' ☐ _____
Air Flow: 1,000 CFM ☐ Variable
Air Changes/Hour: 5
Floor Drains: ☐ Capped ☐ Flushing ☒ Other
Water: ☒ Hot ☒ Cold ☐ None ☐ No ☐ Make-up
Central Vacuum Cleaning: ☐ Yes ☒ No
Local Exhaust Filtration: ☒ Yes ☐ No
Epoxy Coated: ☐ Walls ☐ Floors ☐ Ceilings
Sprinklers: ☐ Yes ☐ No ☒ Halon ☐ Optional
☐ Timed Lighting
☒ Compressed Air: ☒ Vacuum: ☐ Other Gases
☒ Emergency Shower/Eye Wash

SPECIAL FEATURES/BENEFITS

HEPA and charcoal exhaust filter in central article storage area.

SPECIAL ASSUMPTIONS

None.

COST ESTIMATE

	Total $(000)	Resulting $/Sq. Ft.
General Construction	20	15
Heat. Vent., Air Cond.	12	9
Electrical	12	9
Sanitary	7	5
Equipment	166	123
Total	217	161

TITLE Quality Assurance Laboratory — **NO.** 23

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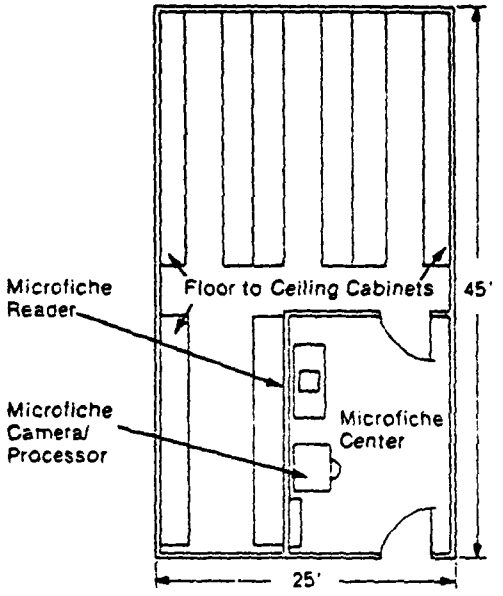
FIGURE 3 QUALITY ASSURANCE LABORATORY

MAMMALIAN TOXICOLOGY FACILITY MODULE DESCRIPTION

Life Systems

FLOOR PLAN



SCALE: 1" = 15'

CONSTRUCTION INFORMATION

Dimensions: 25 x 45 Ft.
Area: 1,125 Sq. Ft.
Ceiling Height ☐ 8' ☒ 9' ☐ 13' ☐_____
Air Flow: 2,530 CFM ☐ Variable
Air Changes/Hour: 5
Floor Drains: ☐ Capped ☐ Flushing ☐ Other
Water: ☐ Hot ☐ Cold ☒ None ☐ No ☐ Make-up
Central Vacuum Cleaning: ☒ Yes ☐ No
Local Exhaust Filtration: ☐ Yes ☒ No
Epoxy Coated: ☐ Walls ☐ Floors ☐ Ceilings
Sprinklers: ☐ Yes ☒ No ☐ Halon ☐ Optional
☐ Timed Lighting
☐ Compressed Air ☐ Vacuum; ☐ Other Gases
☐ Emergency Shower/Eye Wash

SPECIAL FEATURES/BENEFITS

Microfilm-based storage system maximizes storage capacity, control of records and accessibility of information.

SPECIAL ASSUMPTIONS

Microfilm record storage system will be used.

COST ESTIMATE

	Total $(000)	Resulting $/Sq. Ft.
General Construction	15	13
Heat. Vent., Air Cond.	8	7
Electrical	7	6
Sanitary	3	3
Equipment	36	32
Total	69	61

TITLE Record Archives Area

NO. 40

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FIGURE 4 RECORD ARCHIVES AREA

Located nearby are the control article storage area and the refrigerated standard storage area. These areas are designed with air filtration systems to maintain the accuracy of standards and control articles.

Record Archives Area

This area is arranged to safely and efficiently store data and records. As indicated in Figure 4, provisions have been planned for a microfile document storage system to cost-effectively store the large amount of documentation required by the QA program. The Record Archives Area is constructed with flame-resistant walls and contains floor-to-ceiling shelves for safe document storage.

EQUIPMENT AND CONSUMABLES

Equipment

Table 2 is a list of equipment which will be required by the Quality Assurance Laboratory. The primary items which are necessary for functioning of the Quality Assurance Laboratory are gas chromatograph, liquid chromatograph, atomic absorption spectrophotometer, UV/visible spectrophotometer, pH meter, analytical electronic balance, balance table, constant temperature bath and circulating constant temperature bath, freezers, portable hoods and magnetic stir/hot plates. Additional support equipment such as muffle furnaces, titrators, Soxhlet extractors, etc., is available from the Analytical Chemistry Laboratory within the AMTR Facility.

Standard Reference Equipment

The QA Laboratory will require various pieces of standard reference equipment, such as weights (Class S), volumetric flasks (Class A), thermometers and a wide variety of calibration standards for selected analytical methods and instruments, and NBS standard reference samples.

Weights and measures can be obtained from a number of commercial suppliers. However, certification must be done through a State or local agency. In California, certification is done by the Los Angeles County Department of Weights and Measurements. Thermometers are certified by the Metrology Lab, Measurements Standards Division, California Department of Food and Agriculture.

Consumables

Table 3 lists the consumable items which equip a typical QA Laboratory. These include glassware, reagents and solvents, gases and chemicals and miscellaneous items. All consumables other than glassware should include expiration dates.

Management Information System

The Management Information Systems (MIS) is a comprehensive, computer-based information system which includes (Taylor 1980):

TABLE 2 QUALITY ASSURANCE LABORATORY EQUIPMENT LIST

Date 2/10/81
Complete by G. Podrebarac
Area Laboratory No. 23
Title Quality Assurance Laboratory

Equipment List

Equipment Item	Function	Estimated Cost ($000)(a)	Operator Title	Capacity of Equipment (Throughput per unit of time)(b)	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs	Wt. (lbs)	Dimen.(c) (in.)		
Infrared Spectrophotometer 1	Organic analysis	18±2.0	Infrared analytical chemist	25/day	1		X	150-280	Variable	110	NA
Constant Temperature Bath 1	Maintain water at constant temperature	1.0± 0.30	Analytical chemist	Variable	1		X	60	36x16x16	110	Sink
pH Meter 1	Measurement of pH (acid-base)	1.0± 0.20	Analytical chemist	Variable	2		X	10	14x10x10	110	Periodically purchase new electrodes
Balance, analytical (electronic) 1	Accurate gravimetric measurement of materials	6.0±1.0	Analytical chemist	Variable	1		X	30	18x12x10	110	NA
Balance Table 1	Special table, shock resistant for holding balance	0.70± 0.20	Analytical chemist	NA	1		X	60	40x28x18	NA	NA
Constant Temperature Circulating Bath 1	Maintain constant water temperature at remote location	4.0± 0.60	Analytical chemist	Variable	1		X	15	14x12x8	110	Water and sinks

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

continued-

Table 2 - continued

Equipment List

Date 2/10/81
Complete by G. Podrebarac
Area Laboratory No. 23
Title Quality Assurance Laboratory

Equipment Item	Function	Estimated Cost ($000)(a)	Operator Title	Capacity of Equipment (Throughput per unit of time)(b)	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs	>10 yrs	Wt. (lbs)	Dimen(c) (in.)		
Gas Chromatograph (electron capture FID/F-N-P) 1	Organic analysis	12±3.0	Analytical chemist Gas Chromatograph operator	90/day	1	X		250	30x30x30	220	Venting for exhaust gases, space for carrier & detector gases, licensing for nickle 63 radioactive detector (electron capture).
Liquid Chromatograph (analytical) (variable UV, & fluorescence detector) 1	Organic analysis	14±3.0	High performance liquid chromatography analytical chemist	30/day	1	X		Variable	36x36x36	110	NA
Atomic Absorption Spectrophotometer (flame, flameless & graphite furnace) 1	Inorganic analysis	23±3.0	Atomic absorption analytical chemist	30/day	1	X		300	40x18x20	220	Vented hood for exhaust gases
UV Visible Spectrophotometer 1	Specific wave length or variable wave length detection of organic material; also quantitative determination of primary organics	18±10	UV Visible analytical chemist (Any trained analytical chemist should be able to use this)	20/day	1	X		275-350	Variable	110	NA

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

continued-

Table 2 - continued

Equipment List

Date 2/10/81
Complete by G. Podrebarac
Area Laboratory No. 21
Title Quality Assurance Laboratory

Equipment Item	Function	Estimated Cost ($000)(a)	Operator Title	Capacity of Equipment (Throughput per unit of time)(b)	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.(c) (in.)		
Hood 1	Handling chemicals	7.0	Technician	NA	1		X	180	36x48x48	110	NA
Additional Equipment 1	Miscellaneous small items to completely equip area	3.9	Technician	NA	Variable			Variable		110 or NA	NA

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

TABLE 3 LIST OF CONSUMABLES FOR QUALITY ASSURANCE LABORATORY

Glassware

- Separatory funnels
- Graduated cylinders
- Beakers (variable sizes)
- Erlenmeyer flasks
- Snyder condensers
- Kuderna-Danish evaporators
- Thin layer chromatography tanks
- Assorted sizes of vials and caps with Teflon liners
- Ampoules
- Assorted petri dishes
- Watch glasses
- Chromatography columns
- Funnels

Reagents and Solvents

- Hexane (nanograde)
- Acetonitrile (nanograde)
- Isooctane (nanograde)
- Tetrahydrofuran
- Dimethylformamide
- Dichloromethane
- Ester
- Ethanol
- Isoproponol
- Hydrochloric acid
- Nitric acid
- Sulfuric acid

Gases

- Helium (ultrapure)
- Nitrogen (ultrapure)
- Hydrogen
- Oxygen
- Argon-methane

Chemicals and Miscellaneous

- Sodium sulfate
- Sodium hydroxide
- Silica gel
- Florisil
- Sodium chloride
- Potassium chloride
- GC syringes
- LC syringes
- Filter paper
- Septa

1. A recordkeeping (clinical) system
2. A comprehensive data base
3. An integrated data processing system

The MIS must be comprehensive and operate in real time. Some characteristics of a typical MIS are:

1. Immediate recording of any transaction or change

2. Complete data base (historic and current) with decision-making rules

3. Continuous monitoring of the impact of internal and external events which are called to the immediate attention of concerned parties

4. A hierarchy of record output, including periodic and special reports (on request)

5. Decision models and files structured so that significant relationships can be discovered by man-machine interaction

The types of uses the QA would have for MIS are as follows:

1. Compilation of a comprehensive data base for:

   a. Test article log in and distribution
   b. Control article log in and storage site
   c. Equipment calibration
   d. Equipment maintenance charts and schedules
   e. Animal body weights
   f. Clinical and analytical chemistry data, etc.

2. Immediate update capability of any information such as regulatory changes, SOP modifications, protocol changes, etc.

3. Periodic (scheduled) update capability.

4. Information distribution.

The MIS capability should be facility-wide and the QA Department should only be a user of this capability. This type of system will greatly reduce the cost of trail audits and other QA duties.

SCHEDULE AND COSTS

This section of the QA Plan is broken down into four segments: startup, imple mentation and verification, update requirements, and operational requirements.

Startup

The startup phase is basically covers implementing the QA Plan which consists of the following:

- Identify and prepare specific QA SOP's
- Hire QA personnel
- Procure equipment, supplies and consumables and set up the QA Laboratory

The identification and preparation of SOP's will require approximately 14 months from time t = 0 (i.e., the contract start date). This estimate is based on the preparation of an average of 13 SOP's per month. There are at least 185 SOP's which require preparation. The start-up time can be reduced dramatically, perhaps by as much as six months or possibly more, if the facility operator has an ongoing QA/GLP program complete with SOP's. In this case the major thrust would be modification of existing QA procedures rather than preparation of new procedures.

Personnel hiring priority and schedule are as follows:

- QA Manager at time t = 0
- QC Chemist(s) within four months of time t = 0
- QA Inspection Supervisor(s) within four months of time t = 0
- QA Facility Inspector(s) within eight months of time t = 0
- QA Equipment Inspector(s) within 14 months of time t = 0
- QA Audit Inspector(s) within 24 months of time t = 0
- Data and Specimen Archives Supervisor(s) within 24 months of time t = 0

Startup costs are divided into two categories: (1) equipment and supplies and (2) labor. Equipment costs (see Figures 3 and 4) are expected to be approximately $202,000. Supplies cost are estimated to be approximately $37,000.

Labor hours based on the above hire-in times for a 14-month startup period will be about 6,860 person-hours. Assuming an average labor rate of $10 per hour labor costs should be about $68,600 not including overhead and benefits.

Total costs estimated for the startup period are estimated at $307,600.

Implementation and Verification

This phase of the schedule consists of a series of indoctrination lectures on QA, GLP's, and a test of the QA system by using a series of acute, subchronic, chronic and special toxicology studies. This segment may require 26 months or possibly longer.

Facilities inspections, equipment inspections, calibration and checkout, and the consumables testing program will also take place during this time period. In addition, the analytical chemistry proficiency testing program should be

initiated. The facility should be inspected by FDA and EPA GLP inspectors after the completion of the acute and subchronic test series, which should be approximately 22 months after time t = 0.

Costs of this phase is primarily labor and is estimated at 5% of the total cost (see Operational Requirements) of the Facility's operating budget. This does not include costs of conducting the toxicology studies.

Update Requirements

This is an ongoing situation whereby all SOP's are periodically reviewed at six-month intervals. Any additions, deletions or modifications can be made to accommodate any regulatory changes.

A Facility MIS would aid updating efforts by providing for immediate update and notification of changes in any type of information (see Equipment and Consumables, MIS).

Operational Requirements

The operational requirements for QA consist of an ongoing program of inspection and audits of each and every toxicology study which is initiated at the AMTR Facility, as well as continuing the QA/QC program for materials, equipment, performance, traceability, test and control articles. The overall cost impact of the update and operational requirements is approximately 5-6% of the total operating budget of the Facility. Estimates obtained from Raltech (2-3%) and MRI (4-5%) do not include QC costs but only costs for GLP compliance. Therefore, the AMTR Facility QA costs may be higher because of an expanded QC capability.

POTENTIAL PROBLEM AREAS

Personnel and Management Attitudes

The acceptance of QA by technical personnel is a potential problem. Every effort should be made to assure technical personnel that QA is intended to benefit, not detract from, their individual study areas. Management must take an active part in QA affairs and in promoting the attitude of understanding and acceptance among technical staff. QA Personnel must also help to persuade technical staff members that the QA procedures are intended to help, not hinder, prospective programs. This can be minimized by informing the technical people that the QA aspect will help them by systematizing the performance of studies thus making their job more organized and more accepted by outside reviewers.

Although it is not a requirement of the GLP, it will be important for the AMTR Facility to develop an overall QA program that includes GLP compliance as part of its basic framework. Otherwise, regulatory confusion will arise that will affect not only the Facility itself, but also its sponsors and even the FDA and EPA as they carry out their Facility inspections.

A problem common to any QA system is how to measure if it is working as intended. Care must also be taken that there is not QA overkill, a situation in which there is a role reversal between the study performers and the QA personnel.

The Facility and Prime Contractor management should stay alert to this possibility and take steps, if needed, to keep the conduct of research and the QA functions in proper perspective.

Facility Construction Delays

Delays in the construction of the Facility would result in delays in the preparation of certain QA SOP's that require information about the Facility. Also, the test phase and overall implementation/verification of the QA Program would be delayed.

If there should be a serious delay in implementing the QA Plan, it would also delay startup of the AMTR Facility's operations because the toxicological studies cannot begin without a functioning QA Department and QA SOP's. Therefore, it will be important to ensure that all of the QA startup and implementation activities remain on schedule.

CONCLUSIONS

The major functions, responsibilities and organization within the QA Department have been defined. The specific number of people required within the QA Department will vary, depending upon two factors: (1) the size of the AMTR Facility in terms of the number of studies performed and (2) the availability of in-house technical and administrative personnel who are available to perform some of the QA functions. Also, the availability of outside vendors, who can perform some analytical measurements and provide other QA services, can also reduce the number of QA personnel required.

The optimum number of QA personnel, therefore, cannot be defined until the planning of the AMTR Facility organization and testing programs are completed, and the location of the Facility selected (to permit identification of acceptable vendors in the vicinity). However, the personnel functions within the QA Department have been defined.

The initial actions required by the QA Department (preparation of QA SOP's, preparation of procedures for SOP preparation (to be used by other technical staff) and review and validation of SOP's) have been outlined. Approximately 200 SOP's to be required by the AMTR Facility have been identified.

Facilities, equipment and major types of consumables have been identified. A schedule has been prepared that projects a startup period of 14 months and 26 months for implementation and verification of the QA program. The cost of the QA program has been estimated at $307,600 for the first 14 months, and about 5-6% of the operating budget of the AMTR Facility thereafter.

RECOMMENDATIONS

1. The AMTR Facility should develop an overall QA program in which GLP compliance is a subset. The development of a QA Department and QA program whose sole function is GLP compliance is not desirable or efficient.

2. An important criterion for selecting a manager/operator for an AMTR Government Owned Contractor Operated (GOCO) Facility would be that it

have QA and scientific SOP's suitable for adaption to the AMTR Facility's requirements. If possible, it would be desirable that the manager/operator also have an existing QA/GLP program which has passed GLP inspection.

3. Maximum use should be made of either outside support services or the Facility's research scientists and equipment in carrying out the QA program. This approach is cost-effective in that it avoids duplication of personnel and acquisition of costly, infrequently used equipment.

4. Although the QA Department would not be the principal user of an MIS, it will be one of the heaviest users. Its MIS needs should be carefully considered when specifying and justifying acquisition of, or improvements to, a MIS capability.

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APPENDIX 1

STANDARD OPERATING PROCEDURE FOR PREPARING SOP'S
(Prepared by Col. Alfred M. Allen, M.D. 26 March, 1980)

ORGANIZATION HEADING

File No. _____ Date Prepared (or Revised) _____

Title

1. Purpose: (Purpose of the SOP and of the procedure itself.)

2. Scope: (Whom is the SOP for? What does the procedure apply to?)

3. Authority: (Regulation or directive that calls for procedure to be performed.)

4. Procedure:

   a. - z. (Subheadings: Use to break procedure up into major subprocedures or major components.)

5. References:

_____
Signature of preparer

_____
Signature of approving official

Preventitive Medicine Activity
Brooke Army Medical Center
Ft. Sam Houston, Tx 78234

File No. A-1 26 March 1980

SOP for Writing SOP's

1. Purpose: The purpose of this SOP is to show how to write an SOP. SOPs (Standard Operating Procedures) are written, step-by-step guides to carrying out a procedure that are useful in training new employees, ensuring standardization of performance, and keeping management informed of how things are done.

2. Scope: This SOP applies to all organization sections of the Preventive Medicine Activity, Brooke Army Medical Center, Ft. Sam Houston. It should be used as a guide whenever new SOPs are written or existing SOPs are revised.

3. Authority: Not applicable.

4. Procedure:

a. Preparing to Write:

(1) When the writer is informed that an SOP is required, he first checks to see if there is an existing SOP that can be rewritten.

(2) Next, the writer gathers reference materials relating to the procedure in question (instruction manuals, regulations, blank forms, etc).

(3) The writer also determines whether other agencies perform the same procedure; if so, he calls or writes to request a copy of their SOP for reference.

b. Writing:

(1) Upon completion of the above-mentioned preparation to write, the writer selects a suitable format for the SOP. The format presented in the guide entitled How to Write an SOP is suitable for most SOP's, and should be used where possible to ensure uniformity.

(2) Having selected a format, the writer prepares a draft of the SOP using the format selected. Any blank forms used in the procedure are included as annexes to the SOP.

(3) The writer revises and rewrites the draft SOP until it is ready for review; then he has it typed in final form for review.

c. Review, Approval, and Distribution:

(1) Prior to sending the draft SOP out for formal review, the writer reviews the draft for technical adequacy and makes any corrections necessary. Whenever possible, the writer gives the draft to a knowledgeable fellow employee for a second review for technical adequacy.

(2) When the draft SOP has been reviewed for technical adequacy and any necessary corrections made, the writer signs it and requests that it be reviewed for administrative adequacy by his supervisor.

(3) The supervisor reviews the draft SOP to see if it is correct from the administrative point of view (format, correct identification of employees involved, logical sequences of steps, etc.).

(4) If the draft SOP is administratively and technically correct, the supervisor (or officer in charge) dates and signs it, and assigns a file number. If the draft SOP is not correct, the supervisor returns it to the writer for necessary corrections before signing it.

(5) The supervisor furnishes copies of the final signed and dated SOP to the employees involved. The supervisor retains a copy for his files and places a copy in the Central Office files for ready reference.

5. References: Not applicable.

ALFRED M. ALLEN, M.D.
COL, MC
C, Preventive Medicine Activity

Preparer

APPENDIX 2

SAMPLE FORMAT FOR THE PREPARATION AND CONTENT OF STANDARD OPERATING PROCEDURES

Subject: Procedures for Preparation and Update of Standard Operating Procedures (SOPs)

Department: Quality Assurance

Code No.: _____

Date: _____

Page: ____ of ____

Approved by: _____
Title: _____

Approved by: _____
Title: _____

Approved and
Released by: _____
Title: _____

Revision: _____

I. Standard Operating Procedure (SOP) is herein defined as a detailed set of written directions and/or specifications for laboratory Quality Assurance operations.

II. Format requirements for SOPs:

A. Title of the Procedure

B. Department issuing Procedure

C. Code number

D. Date of issue

E. Number of pages

F. Signature of the approvers

G. Signature of Quality Assurance giving approval of release

H. Revision number

III. General Provisions and Criteria:

A. Points of consideration for SOP preparation.

1. SOPs must be easily understood by the user.

2. Descriptions, directions or details shall be complete, brief and precise.

3. Any forms referred to in the text shall be appended.

B. Quality Assurance Manager's Responsibilities for SOP preparation, issue and maintenance.

1. Identifies, compiles and writes the SOP;

2. Monitors and assures conformance of practice to the SOP;

3. Makes appropriate SOPs available to study personnel;

4. Reviews, amends and updates SOPs on a semi-annual basis;

5. Issues SOPs and amendments to Quality Assurance Department personnel, Study Directors and Director of Toxicology Testing/ Research and Director of Support Services;

6. Keeps master sets of SOPs, including originals and amendments on file;

7. Approves each SOP for release.

C. SOP and all amendments must be signed by the Director of Toxicology Testing/Rsearch, Director of Support Services and Quality Assurance Manager.

D. The SOP is released for issue by Quality Assurance and becomes an operating part of the QA Manual.

APPENDIX 3

A LIST OF TITLES FOR QUALITY ASSURANCE STANDARD OPERATING PROCEDURES

Specific titles of SOPs are given under the following major headings:

- Facilities Specification
- Facilities Inspection and Sanitation
- Equipment Inspection
- Equipment Maintenance
- Equipment Calibration
- Consumables Acceptability
- ADPE
- Record Storage
- Traceability
- Test and Control Article
- Performance Audit
- Corrective Action
- Study Planning and Conduct
- Personnel
- Animal Care

Facilities Specification Standard Operating Procedures

- Analytical and Synthetic Chemistry Laboratory
- Animal Care Facilities
- Animal Care Supplier Facility
- Animal Surgery Facilities
- Animal Quarantine Area
- Cage/Rack Washing Area
- Control Article Storage Facilities
- Control Article Handling Facilities
- Feed Mixing and Blending Area
- Glass Washing Area
- Inhalation Exposure Area (with special reference to smokes and obscurants)
- Pathology Laboratory
- Radiochemistry Laboratory
- Refrigerated Food Storage Area
- Showers/Dressing Room
- Test Article Storage Facilities
- Test Article Handling Facilities
- Waste Handling and Disposal Area
- Veterinary Medicine Area

Facilities Inspection and Sanitation Standard Operating Procedures

- Analytical and Synthetic Chemistry Laboratory
- Animal Care Facilities
- Animal Care Supplier Facility
- Animal Surgery Facilities
- Animal Quarantine Area

- Cage/Rack Washing Area
- Control Article Storage Facilities
- Control Article Handling Facilities
- Feed Mixing and Blending Area
- Glass Washing Area
- Inhalation Exposure Area
- Pathology Laboratory
- Radiochemistry Laboratory
- Refrigerated Food Storage Area
- Showers/Dressing Room
- Test Article Storage Facilities
- Test Article Handling Facilities
- Waste Handling and Disposal Area
- Veterinary Medicine Area

Equipment Inspection Standard Operating Procedures

- Aerosol Generation System (Inhalation Chamber)
- Animal Cage
- Animal Racks
- Atomic Absorption Spectrophotometers
- Autotechnician Tissue Processor
- Automatic Titrator
- Balance (Analytical)
- Balance (Top Loader)
- Constant Temperature Bath
- GC Autosampler
- Gel Permeation Chromatograph
- Gas Chromatographs (and Detectors)
- Infrared Spectrophotometer
- Inhalation Chambers
- Liquid Chromatographs (and Detectors)
- Microscope
- Miscellaneous Glassware
- Muffle Furnace
- pH Meter
- Thin Layer Chromatograph Scanner
- UV Visible Spectrophotometer
- Vapor Generation System (Inhalation Chamber)

Equipment Maintenance Standard Operating Procedures

- Aerosol Generation System (Inhalation Chamber)
- Animal Cage
- Animal Racks
- Atomic Absorption Spectrophotometer
- Autotechnician Tissue Processor
- Automatic Titrator
- Balance (Analytical)
- Balance (Top Loader)
- Constant Temperature Bath
- GC Autosampler

- Gel Permeation Chromatograph
- Gas Chromatographs (and Detectors)
- Infrared Spectrophotometer
- Inhalation Chambers
- Liquid Chromatographs (and Detectors)
- Microscope
- Miscellaneous Glassware
- Muffle Furnace
- pH Meter
- Thin Layer Chromotograph Scanner
- UV Visible Spectrophotometer
- Vapor Generation System (Inhalation Chamber)

Equipment Calibration Standard Operating Procedures

- Aerosol Generation System (Inhalation Chamber)
- Atomic Absorption Spectormeter
- Automatic Titrator
- Balance (Analytical)
- Balance (Top Loader)
- GC Automsampler
- Gel Permeation Chromatograph
- Gas Chromatograph
- Infrared Spectrophotometer
- Inhalation Chambers
- Liquid Chromatographs
- pH Meter
- UV Visible Spectrophotometer
- Vapor Generation System (Inhalation Chamber)

Consumables Acceptability Standard Operating Procedures

- Animal Quality Testing - Dogs
- Animal Quality Testing - Guinea Pigs
- Animal Quality Testing - Hamsters
- Animal Quality Testing - Non-Human Primates
- Animal Quality Testing - Mice
- Animal Quality Testing - Rabbits
- Animal Quality Testing - Rats
- Chemical Quality Testing
- Gas Quality Testing
- Reagents and Solvents Quality Testing

ADPE Standard Operating Procedures

- ADPE Data Entry Operator Identification
- ADPE Data Storage and Retrieval
- ADPE Operator Training
- ADPE Inspection and Maintenance
- ADPE Audit
- ADPE Error Correction Authorization
- ADPE Data Checkpoint

- Error Notification and Correction
- Data Cross Verification
- Data Input Verification and Editing
- Data Collection and Transcription
- Data Format Input
- Data Format Output
- Instrument Diagnostic
- Statistical Analysis Test Verification for ADPE

Record Storage Standard Operating Procedures

- Computer Tape and Disc Storage
- Data Storage and Retrieval
- Data and Specimen Retention Requirement
- Data Transfer to Repository
- Data Storage (Repository) Security
- Preserved Tissue Storage and Retrieval
- Tissue Block Storage and Retrieval
- Tissue Slide Storage and Retrieval

Traceability Standard Operating Procedures

- Control Article
- Data Trail Audit
- Test Article
- Test System (Animal)

Test and Control Articles Standard Operating Procedures

- Control Article Handling
- Control Article Dose Preparation (Weighing and Mixing)
- Determination of Control Article Identity
- Determination of Control Article Strength, Purity and Composition
- Determination of Control Article Stability
- Determination of Control Article Dose Homogenity
- Determination of Test Article Identity
- Determination of Test Article Strength, Purity and Composition
- Determination of Test Article Stability
- Determination of Test Article Dose Homogeneity
- Test Article Dose Preparation (Weighing and Mixing) Procedure
- Test Article Handling Procedure

Performance Audit Standard Operating Procedures

- Preparation of Performance Audit Sample
- Performance Audit Sample Identification and Routing
- Performance Audit Sample Traceability
- Reporting of Performance Audit Results of Quality Assurance
- Reporting of "Out of Control" Performance Audit Results to Management

Corrective Action Standard Operating Procedures

- Report to Management
- Corrective Action

Study Planning and Conduct Standard Operating Procedures

- Computer Data Entry Operator Identification
- Master Study List Maintenance
- Notebook Data Recording and Initializing
- Notebook Data Entry Change
- Protocol Preparation
- Protocol Change
- Pre-Study Personnel Training (and Instruction)
- Specimen Identification
- Study Director Designation Procedure
- Study Director Replacement
- Study Inspection
- Study Credit
- Test System (Animal) Identification

Personnel Standard Operating Procedures

- Background Summary (CV) Preparation
- Illness Notification to Supervisor and Exclusion from Study
- Personnel Training
- Personnel Clothing and Safety
- Personnel Health and Sanitation

Animal Care Standard Operating Procedures

- Animal Bedding and Cage Changing
- Animal Cage Identification
- Animal Identification: Mice, Rats, Guinea Pigs and Hamsters
- Animal Identification: Rabbits
- Animal Identification: Dogs
- Animal Identification: Non-Human Primates
- Animal Handling, Feeding and Watering: Rats and Mice
- Animal Handling, Feeding and Watering: Rabbits
- Animal Handling, Feeding and Watering: Dogs
- Animal Handling, Feeding and Watering: Non-Human Primates
- Animal Room Sanitation
- Animal Cage and Rack Cleaning and Sanitizing: Stainless Steel Cages
- Animal Cage and Rack Cleaning and Sanitizing: Plastic Cages
- Animal Cage and Rack Cleaning and Sanitizing: Stainless Steel Cage Racks
- Animal Feeder Cleaning
- Animal Drop Pans Cleaning and Sanitizing
- Blood Sampling in Rats, Mice and Rabbits
- Blood Sampling in Dogs
- Blood Sampling in Non-Human Primates
- Determination of Animal Health
- Euthanasia - Rodents and Rabbits
- Euthanasia - Dogs

APPENDIX 4

A Standard Operating Procedure" Audit of Project Reports" from Paget, G.E. and Thomson R. "Standard Operating Procedures in Toxicology," University Park Press, Baltimore, MD 1979

AUDIT OF PROJECT REPORTS

1. INTRODUCTION

1.1 The aims of a report audit are,

1.1.1 to confirm that a study was performed in accordance with the agreed protocol

1.1.2 to ensure that the study is accurately and complete reported,

1.1.3 to check that the minimum required contents (see SOP/REC/007, section 2) are present,

1.1.4 to check that the report is internally consistent.

1.2 Auditors should satisfy themselves that these aims are fulfilled rather than working by rote through any specific checklist. The typical audit detailed in section 2, below should serve only as a guide.

1.3 A report will normally be audited at the draft report stage, in the six-week period allowed for the client to approve the draft before final issue. Thus, a copy of all draft reports must be issued to the Quality Assurance Manager.

1.4 Where longer than six weeks is required for audit or where no draft report is issued, audit of the final report must be individually arranged with the Quality Assurance Manager by the Principal Investigator or Project Leader.

1.5 On receipt of a report for audit the Quality Assurance Manager must assign responsibility for the audit, indicating the approximate time allowed. He/she should at the same time request the complete project archive from the Project Leader.

2. TYPICAL REPORT AUDIT

The following guidelines give examples of items which might be covered in a typical audit. They should not be regarded as comprehensive or obligatory. A given audit may be extended or even curtailed if it is felt appropriate. Similarly, the order of working may be varied to suit a particular auditor or a particular project.

2.1 Check that the start and completion dates in the original data and the report agree.

2.3 Selecting each type of data in turn, e.g. haematology, check that the data in the report are correctly identified and that they were collected at the times required by the protocol.

2.4 Check that the original data correspond with the data in the report. This should be done on a sampling basis. The sampling rates should be as follows,

2.4.1 Observations which may individually be regarded as critical to the interpretation of the study, e.g., clinical observations of animals, pathological findings, macroscopic and microscopic, 100% check.

2.4.2 Observations which are less critical individually to the interpretation of the study, e.g., bodyweights, clinical chemistry results, 10% random check. A ten percent random check should be performed by checking one column or row from every ten using a random number table to indicate which of the ten is to be chosen. This routine may be extended or modified if it is felt appropriate to check areas with a higher probability of errors.

2.4.3 For summarized or reduced data the same criteria of checking apply. It will normally also be necessary to follow through data reductions or calculations. This may be deemed unnecessary if calculations are made from a data base using a proven computer programme with a hard copy of input available.

In this case only the input data and final reported results need to be checked.

2.5 Check the text of the report to ensure that the experiment and its execution are accurately described and that its execution complied with the protocol and appropriate Standard Operating Procedures. Under this heading should be included the checking of dates, times and time periods, the preparation, administration and control of test substance, the receipt and acceptance of animals, the records of batches of diet used, etc.

2.6 Check that any divergence from protocol or Standard Operating Procedures has been fully authorized and documented.

2.7 Check that there is appropriate commentary on any unforeseen or untoward occurrences during the experiment.

2.8 Check the data and the text of the report for consistency and for mutual and self-compatibility. This includes, checking on unplanned deaths in the study and the record keeping subsequent to them, checking the follow-up on unexpected observations or happenings, etc.

2.9 Finally, use should be made of the quality control inspections carried out during the study to check for appropriate action being taken subsequent to these.

3. RECORD KEEPING

3.1 The audited copy of the draft report should be marked "Quality Assurance Audit Copy." Data checked should be ticked by piece or by column and any errors found should be indicated.

3.2 Following audit a report should be prepared using a Quality Assurance Inspection Record (QAU/003, Appendix I). This should indicate the page, appendix or portion of the report audited, the data checked, and the error rate found. It should also include a description of other data errors and other comments as necessary. The report must be signed and dated by the auditor(s).

3.3 In addition, a summary page must be prepared detailing any recommendations following auditing.

The Quality Assurance Manager must sign this page indicating whether he/she is prepared to sign the final report.

3.4 The Quality Assurance report must be sent with the summary page to the Principal Investigator for comment and/or action.

3.5 Following any such action further checking may be required by the client or the Quality Assurance Unit. The extent of such rechecking will depend upon the extent of any changes made to the report.

3.6 Finally, when the report is deemed satisfactory, the Quality Assurance Manager is in a position to sign the Quality Assurance Authentication page to be included in the final report (Appendix II).

APPENDIX 5

TABLE OF CONTENTS OF THE QUALITY ASSURANCE MANUAL

continued-

Appendix 5 - continued

Table of Contents - continued

DISTRIBUTION LIST

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